REMARKS

Applicant acknowledges that the Examiner has deemed the requirement for restriction final. Accordingly, claims 17-23 are withdrawn from further consideration in the present application. Claims 2, 3, and 5 are canceled herein. Claims 1, 4, 6-16 and 24-28 are, therefore, presently under consideration. Claims 1, 4, 6-8, 11, and 24-26 have been amended to more clearly set forth aspects of the invention. New claims 29-33 are presented herein. Accordingly, claims 1, 4, 6-8, 11, and 24-26 as amended, and dependent claims therefrom, and new claims 29-34 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 1 is presented, for example, in original claims 1 and 5 and in the specification, for example, at paragraphs [0027], [0033], [0081], and [0088]. Support for amendments to claims 6-8 is found in original claims 6-8 and in paragraphs [0034], [0035], [0045], and [0084]. Support for amendment to claim 24 is found in original claims 5, 19, and 24 and in the specification at paragraph [0081]. Support for amendments to claims 4, 11, 25, and 26 is found in original claims 4, 11, 25, and 26. No new matter is introduced by the amendments to the claims.

Support for new claims 29-34 is found throughout the specification and in the original claims. Specifically, support for new claim 29 is found in original claim 14; support for new claim 30 is found in original claim 1; support for new claim 31 is found in original claims 1 and 14; support for new claim 32 is found in original claims 1, 2, and 14; support for new claim 33 is found in original claims 1, 3, and 14; and support for new claim 34 is found in original claims 1, 5, and 14. No issue of new matter is hereby introduced.

Information Disclosure Statement

The Examiner has indicated that a copy of the WO 01/04313 A1 application, which was designated as BG in the Information Disclosure Statement (IDS) filed 6/30/2005, was allegedly not provided. Applicant believes that a copy of this reference was submitted to the United States Patent and Trademark Office with the IDS in

question. To be fully responsive to the Examiner's request, however, a copy of WO 01/04313 A1 is enclosed herein for the Examiner's consideration.

Oath/Declaration

The Examiner has pointed out certain problems with the previously submitted Declaration that render it defective. Accordingly, a properly executed Declaration is submitted herewith to rectify the indicated problems.

Sequence Compliance

The Examiner has indicated that a nucleic acid sequence listed in the specification is not referred to by the use of a sequence identifier. In response, Applicant has amended the specification to delete reference to the indicated sequence. Applicant, therefore, believes that the instant specification is compliant with the sequence rules as set forth in 37 CFR 1.821-1.825.

Claim Objections

Claims 19-28 are objected to because they depend from a claim that has been withdrawn. Accordingly, these claims are amended to obviate this objection.

Claims 1-7 and 11 are objected to for use of the phrase "peptide or polypeptide", recitation of both of which the Examiner maintains is redundant. Claims 2, 3, and 5 are canceled herein, thereby obviating any objection to these claims. In response to the objection to the instant claims, Applicant has amended these claims to recite the term "polypeptide", by which is meant a molecule comprising a chain of amino acids that upon hydrolysis yields more than two amino acids.

Provisional Rejections Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1, 2-5, 24, and 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 18 of co-pending U.S. Application No. 11/025,858 in view of Pavlakis et al. (U.S. Patent No. 5,965,726). Claims 2, 3, and 5 are canceled herein, thereby obviating even a provisional

rejection of these claims. In response, however, Applicant offers a willingness to consider filing a Terminal Disclaimer after or upon notification of allowable subject matter in both applications.

Rejections under 35 USC § 112

Claims 1, 6-16, 24, and 25 are rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. Claim 1 is amended herein to recite "wild type mRNA", for which antecedent basis is set forth, rather than "modified wild type mRNA". Claims 24-26 are amended herein to recite an isolated nucleic acid molecule. Applicant, therefore, believes that the amendments to claims 1 and 24-25 are curative of the rejection of claims 1, 6-16, 24, and 25 based on alleged indefiniteness. In view of the above amendments to the claims, Applicant respectfully requests that the rejection under 35 USC § 112, second paragraph, be withdrawn.

Claims 1, 6, and 7 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the written description requirement. This rejection appears to be based on the size of the genus of destabilizing elements encompassed by the claims and alleged deficiencies related to examples presented in the specification. At the outset, claim 1 is directed to a pharmaceutical composition comprising at least one modified mRNA that encodes at least one polypeptide, wherein said modified mRNA encoding the polypeptide comprises an increase in Guanine/Cytosine (G/C) content relative to that of a wild type mRNA encoding the polypeptide, wherein the modified mRNA comprises a maximum G/C content, and the wild type mRNA and the modified mRNA encode a polypeptide comprising an identical amino acid sequence; and wherein said modified mRNA encoding the polypeptide comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, and said abundant and rare cellular tRNAs recognize the same amino acid. Claim 1 makes no reference to a modified mRNA comprising a destabilizing sequence or from which destabilising elements have been deleted. In view of the above, the rejection of claim 1 under 35 USC § 112, first paragraph, appears to be without basis. Accordingly, Applicant asserts that the rejection of claim 1 is improper and respectfully requests that the rejection be withdrawn.

With respect to claims 6 and 7, which are directed to a set of modified mRNA molecules comprising fewer destabilizing elements (claim 6) or no destabilizing elements (claim 7), Applicant offers the following in response to the Examiner's comments. The Examiner focuses repeatedly on the mechanism(s) of how a destabilizing element contributes to mRNA stability, rather than the presence or absence of a destabilizing element. See page 8, last paragraph and page 10, lines 13-20 of the Office Action. Applicant maintains that a reduction or elimination of a destabilizing element or elements identified in a sequence is germane to the claims, whereas a mechanistic understanding of the molecular mechanisms involved in effecting their function is not particularly relevant.

Applicant also asserts that the Examiner's comments pertaining to Pesole et al. (Nucleic Acids Res. 30:335-340, 2002) are interpreted in a manner not entirely consistent with statements actually made in the article. The Examiner, for example, appears to have translated the following statement into acquiring an altered meaning:

> "*Even if statistical significance does not necessarily mean biological significance, it may provide useful indication for further experimental work, such as site-directed mutagenesis.*"

The Examiner appears to have paraphrased this statement, in particular, from the paragraph bridging pages 338-339, to mean "Pesole et al teach that a statistically significant match to a database sequence does not necessarily mean that the sequence has biological significance." Applicant asserts that this is not an accurate interpretation of the authors' statements. Pesole et al. suggest only the possibility that statistical significance may not necessarily relate to biological significance. They offer no evidence indicating that statistical significance does not necessarily relate to biological significance, as suggested by the Examiner.

The Examiner's comments pertaining to Wilusz et al. (2004, Trends in Genetics 20: 495, What next?) also appear to reflect an inappropriate degree of subjective interpretation. Although the authors offer that "we are still a long way from being able to predict how an mRNA will decay based on its sequence", this statement, read in the context of the paragraph in which it appears, is clearly referring to the mechanism by which an mRNA comprising a stability regulating element decays. The effect of the

presence of the stability regulating element in an mRNA is not in question, only the means by which the regulatory influence of the element is put into effect. This stands in marked contrast to the Examiner's interpretation that "prediction of how an mRNA will decay based on its sequence is not possible".

In view of the information available in the art, as exemplified by the extensive database assembled by Pesole et al. (see Nucleic Acids Res. 30:335-340, 2002), Applicant asserts that the prior art does teach a highly representative number of destabilizing elements that would allow the identification of these destabilizing elements and related destabilizing element sequences in any mRNA. A brief review of the website to which Pesole et al. refer readers (See Abstract; http://bighost.area.ba.cnr.it/BIG/UTRHome/) reveals that numerous mRNA destabilizing elements had been reported at around the earliest priority date of the present invention. In this context, it is particularly relevant to attest that it is well accepted that that which is known in the field need not be repeated in the context of a specification. For all of the above reasons, Applicant asserts that the Examiner's rejection of claims 6 and 7 under 35 USC § 112, first paragraph, is flawed.

In the interests of expediting prosecution of claims 6 and 7, however, Applicant is amending these claims to recite types of mRNA destabilizing elements for which the specification presents ample written description. Applicant reserves the right, however, to pursue broader aspects of these claims in other applications.

Claims 1 and 8 have been rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner maintains that claims 1 and 8 are drawn to or encompass a set of modified mRNA comprising 5' and/or 3' stabilization sequences. Applicant asserts that claim 1 makes no reference to a modified mRNA having a stabilization sequence. In view of the above, this rejection of claim 1 under 35 USC § 112, first paragraph, appears to be without basis. Accordingly, Applicant asserts that the rejection of claim 1 is improper and respectfully requests that the rejection be withdrawn.

Claim 8 is amended herein to delete reference to 5' and/or 3' stabilization sequences. Applicant believes that the amendment to claim 8 is, therefore, curative of the rejection and respectfully requests that the rejection be withdrawn.

In view of the clarifying amendments to the claims and the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. § 112, first paragraph, and withdraw the rejection.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 1, 3, 6, 11-15, 24, and 26 under 35 U.S.C. §102(b) as allegedly anticipated by Pavlakis et al. [United States Patent Number (USPN) 5,965,726]. Applicant deferentially disagrees with the Examiner with respect to this rejection. Claim 3 is canceled herein, thereby obviating any rejection of this claim. In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection as it applied to claims 1, 6, 11-15, 24, and 26 is respectfully traversed.

As indicated throughout the document, the invention of the Pavlakis et al. patent is directed to a method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions therein without altering the coding capacity of the gene. This focused approach to removing inhibitory/instability sequences by these means is repeated throughout the patent. Indeed, the passages to which the Examiner has referred are fully supportive of Applicant's understanding of the Pavlakis et al. invention. See column 11, line 45 through to column 12, line 30. The crux of the Pavlakis et al. invention is clearly set forth in the following excerpt from column 12, lines 13-27:

> "*If the INS region is AT rich or GC rich, it is preferable that it be altered so that it has a content of about 50% G and C and about 50% A and T. If the INS region contains less-preferred codons, it is preferable that those be altered to more-preferred codons. If desired, however (e.g., to make an A and T rich region more G and C rich), more-preferred codons can be altered to less-preferred codons. If the INS region contains conserved nucleotides, some of those conserved nucleotides could be altered to non-conserved nucleotides. Again, the only requirement is that the amino acid sequence encoded by the protein remain unchanged; or, if conservative and non-conservative amino acid substitutions are*

to be made, the only requirement is that the protein encoded by the mutated gene be substantially similar to the protein encoded by the non-mutated gene."

Thus, Applicant asserts that the Pavlakis et al. patent is **not** broadly directed to generating a modified mRNA encoding a polypeptide, wherein the modified mRNA comprises an increase in Guanine/Cytosine (G/C) content relative to that of a wild type mRNA encoding the polypeptide, wherein the modified mRNA comprises a **maximum** G/C content, and wherein the wild type mRNA and the modified mRNA encode a polypeptide comprising an identical amino acid sequence; and wherein said modified mRNA encoding the polypeptide comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, and said abundant and rare cellular tRNAs recognize the same amino acid as presently claimed in the instant invention.

In that the Pavlakis et al. patent is particularly directed to introducing point mutations into INS regions (sub-regions of a larger mRNA) and does not teach rendering such mutations **throughout** an mRNA, there is no appreciation of the recited feature of a modified mRNA having maximized GC content. Even with respect to mutating INS regions, Pavlakis et al. teach that if an INS is AT rich or GC rich, it is preferable that the INS be altered to be about 50% GC and 50% AT content. Moreover, it is apparent from the above-quoted passage that the Pavlakis et al. invention tolerates amino acid substitutions resulting from point mutations introduced into INS regions. The presently claimed invention specifically excludes introduction of changes on the level of the modified mRNA that result in alterations in the amino acid sequence of a polypeptide encoded therefrom.

In view of the above, Applicant asserts that the Pavlakis et al. reference does not anticipate the present invention. Indeed, it fails to teach several features of the claimed modified mRNA of the present invention. Applicant, therefore, respectfully requests that the Examiner reconsider the basis for this rejection and withdraw the rejection.

The Examiner has rejected claims 1, 8, 9, and 11-16 under 35 U.S.C. §102(b) as allegedly anticipated by Felgner et al. (USPN 5,580,859). Applicant strenuously disagrees with the Examiner with respect to this rejection. In view of Applicant's

arguments presented herein, therefore, the rejection as it applied to claims 1, 8, 9, and 11-16 is respectfully traversed.

The Felgner et al. patent is utterly devoid of any teaching directed to a modified mRNA having the presently recited features. It is directed to a modified mRNA, such modification including capping the mRNA, circularizing the mRNA, or chemically blocking the 5' end of the mRNA, but it does not teach modified mRNA having altered or maximized GC content and is silent with respect to modified mRNA that comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA. In view of the above, the Felgner et al. patent is defective with regard to at least these two features of the present invention as claimed. Applicant, therefore, respectfully requests that the rejection of the claims based on the Felgner et al. patent be withdrawn.

The Examiner has rejected claims 24 and 26 under 35 U.S.C. §102(b) as allegedly anticipated by Chen et al. (WO 99/20774). In view of the clarifying amendments to the claims and Applicant's arguments presented herein, the rejection as it applied to claims 24 and 26 is respectfully traversed.

In contrast to the Examiner's statement that Chen et al. teach a vaccine comprising a modified nucleic acid sequence with increased GC content and increased frequency of codons recognized by abundant cellular tRNAs, Applicant asserts that Chen et al. actually teach lowering the overall AT content of the natural gene encoding MSP-1 to produce a specific modified nucleic acid sequence, thereby eliminating all mRNA instability motifs, and replacing all rare codons with preferred codons in mammary gland tissue. The application, therefore, appears to be directed to a particular gene, namely MSP-1 of the malaria parasite, and expression of MSP-1 in a particular tissue, specifically mammary tissue. It is not broadly directed to a modified nucleic acid sequence comprising a maximum GC content as presently claimed. Lowering overall AT content is not equivalent to achieving a modified nucleic acid sequence having a maximum GC content, especially within the context of the other recited features of claims 24 and 26. Applicant, therefore, asserts that the Chen et al. application fails to teach at least one recited element of claims 24 and 26.

In view of the clarifying amendments to the claims and the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

Rejections under 35 USC § 103

Claims 1-9, 11-16, 24, and 26-28 are rejected under 35 USC § 103(a) as allegedly unpatentable over Chen et al. (WO 99/20774) in view of Felgner et al. (USPN 5,580,859). Claims 2, 3, and 5 are canceled herein, thereby obviating any rejection of these claims. In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1, 4, 6-9, 11-16, 24, and 26-28, is respectfully traversed.

As described herein above with respect to both Chen et al. and Felgner et al., neither one of these references describes a modified mRNA or a modified nucleic acid sequence having a maximum GC content as presently claimed. To begin, Chen et al. is not broadly directed to a modified mRNA or a modified nucleic acid sequence comprising a maximum GC content as presently claimed. Lowering overall AT content is not equivalent to achieving a modified mRNA or nucleic acid sequence having a maximum GC content. Moreover, in that the step of lowering overall AT content is directed to improving expression of MSP-1, especially in mammary tissue, and is coupled to use of preferred codons utilized in mammary tissue, the reduction in AT content is clearly tempered by codon usage preference in such tissue. Indeed, as stated therein at page 3, lines 14-18:

> *"In a second aspect, the invention provides a process for preparing a modified nucleic acid of the invention comprising the steps of lowering the overall AT content of the natural gene encoding MSP-1,* ***eliminating all mRNA instability motifs*** *and* ***replacing all rare codons with a preferred codon of the mammary gland tissue****, all by replacing specific codons in the natural gene with codons recognizable to, and preferred by mammary gland tissue and which code for the same amino acids as the replaced gene."* Emphasis added.

In view of the above, it is apparent that "eliminating all mRNA instability motifs and replacing all rare codons with a preferred codon of the mammary gland tissue" takes precedence over "lowering the overall AT content". In other words, if eliminating all mRNA instability motifs and replacing all rare codons with a preferred codon of the mammary gland tissue increases the AT-rich character of a nucleic acid sequence, then the effort to lower the AT content is contravened.

With regard to the Felgner et al. patent, this reference is, as described above, particularly defective with respect to at least two of the recited features of the present invention. The Felgner et al. patent does not teach a modified mRNA or nucleic acid sequence having altered or maximized GC content and is silent with respect to a modified mRNA or nucleic acid sequence that comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA.

Since neither Chen et al. nor Felgner et al. teach or suggest a modified mRNA or nucleic acid sequence having a maximum GC content, which further comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, Applicant maintains that these references, when considered either alone or in combination, fail to impact the patentability of the instant invention.

Claims 1, 3, 6, 9-15, 24, and 26 are rejected under 35 USC § 103(a) as allegedly unpatentable over Pavlakis et al. (USPN 5,965,726) in view of Ueda et al. (Nucleic Acids Res. 19:547-552, 1991). Claim 3 is canceled herein, thereby obviating any rejection of this claim. In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1, 6, 9-15, 24, and 26, is respectfully traversed.

As described herein above, the Pavlakis et al. patent is directed to a method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene. Removing inhibitory/instability sequences is, therefore, the focus of the patent. The Pavlakis et al. patent is **not** broadly directed to

generating a modified mRNA or modified nucleic acid sequence encoding a polypeptide, wherein the modified mRNA comprises an increase in Guanine/Cytosine (G/C) content relative to that of a wild type mRNA or modified nucleic acid sequence encoding the polypeptide, wherein the modified mRNA or modified nucleic acid sequence comprises a **maximum** G/C content, and wherein the wild type mRNA or nucleic acid sequence and the modified mRNA or modified nucleic acid sequence encode a polypeptide comprising an identical amino acid sequence; and wherein said modified mRNA or modified nucleic acid sequence encoding the polypeptide comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, and said abundant and rare cellular tRNAs recognize the same amino acid as presently claimed in the instant invention.

In that the Pavlakis et al. patent is particularly directed to introducing point mutations into INS regions (sub-regions of a larger mRNA) and does not teach rendering such mutations **throughout** an mRNA, there is no appreciation of the recited feature of a modified mRNA having maximized GC content. Even with respect to mutating INS regions, Pavlakis et al. teach that if an INS is AT rich or GC rich, it is preferable that the INS be altered to be about 50% GC and 50% AT content. It is also evident that the Pavlakis et al. invention tolerates amino acid substitutions resulting from point mutations introduced into INS regions. The presently claimed invention specifically excludes introduction of changes on the level of the modified mRNA or modified nucleic acid sequence that result in alterations in the amino acid sequence of a polypeptide encoded therefrom. Thus, the Pavlakis et al. patent fails to teach or suggest at least two features of the claimed invention.

Applicant further asserts that the deficiencies of Pavlakis et al. are not remedied by the teaching of Ueda et al. The reference authored by Ueda et al. (Nucleic Acids Res. 19:547-552, 1991) is directed to phosphorothioate-containing RNAs and protein translation therefrom in *in vitro* prokaryotic translation systems. The defects of Pavlakis et al., as set forth above, are not remedied by the disclosure of Ueda et al. Specifically, there is no teaching or guidance relating to a modified mRNA or modified nucleic acid sequence having maximized GC content. Moreover, there is no teaching directed to a modified mRNA having maximized GC content, wherein the modified mRNA encodes a

polypeptide identical to that of the unmodified wildtype mRNA from which it was derived, and which modified mRNA comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, and said abundant and rare cellular tRNAs recognize the same amino acid. In view of the above, the Ueda et al. reference fails to teach or suggest several features of the claimed invention.

Applicant, therefore, asserts that the teachings of these references, when considered either alone or in combination, would not lead a skilled artisan to the presently claimed features of the invention.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §103 and withdraw the rejection.

Fees and Conclusion

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Enclosures: Petition for a Two-Month Extension of Time; Supplemental Information Disclosure Statement; Copy of WO 01/04313 A1; Substitute Declaration and Power of Attorney